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(54) Title A pharmaceutical preparation for improving the resorption of anti-bacterial components

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Description

The present invention relates to pharmaceutical preparations containing (a) an antibacterial compound and (b) an effective amount of an absorption enhancing 2-component system consisting of (b1) polyoxyethylene glycol lauryl ether with 12 ethylene oxide units in the polyoxyethylene glycol part (Laureth-12) and (b2) sodium caprylate. If desired, the preparation in accordance with the invention can also contain a pharmaceutically inert carrier.

Document EP-A-0 126 348 describes formulations for improving the rectal absorption of medicaments, which contain a C_{8-10}-fatty acid or salt thereof and polyoxyethylene (21) lauryl ether. Document EP-A-0 108 295 describes preparations for the enteral absorption of β-lactam antibiotics, which contain as the absorption enhancer a C_{2-18}-fatty acid, a C_{2-12}-fatty acid glyceride, a propylene glycol, a polyethylene glycol or carbohydrate fully or partially esterified with a C_{2-12}-fatty acid, or mixtures thereof. Document EP-A-0 152 896 describes suppositories containing ceftriaxone, which contain as stabilizers C_{2-18}-fatty acid glycerides, C_2-C_{18}-fatty acids, propylene glycol, polyethylene glycol or carbohydrates fully or partially esterified with a C_{2-18}-fatty acid, or mixtures thereof.

It has been found that the above-identified absorption enhancing system leads to an increase in the extent of the adsorption of antibacterial compounds through mucosal tissue and into the bloodstream. The invention thus promotes the adsorption and, concomitantly, the bioavailability of antibacterial compounds which, when administered without the adsorption enhancer by routes other than parenteral, are only poorly absorbed or not absorbed to any appreciable degree. The preparation and use of a greater variety of dosage forms for such compounds are thus enabled. The pharmaceutical preparations in accordance with the present invention also promote the absorption and bioavailability of antibacterial compounds which are otherwise

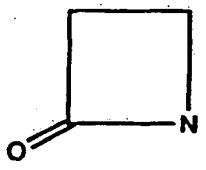
only moderately adsorbed through mucosal tissue and thus also enhance the effectiveness of such therapeutic compounds.

The invention relates to pharmaceutical preparations for administration in any dosage form suitable for oral or rectal administration. There are thus included oral and rectal types of pharmaceutical preparations containing effective amounts of an antibacterial compound and of the absorption enhancing system in accordance with the invention, with or without an inert carrier and pharmaceutically usable adjuvants.

The terms "antibacterial" and "antibiotic" are used interchangeably herein and denote bactericidal or bacteriostatic compounds which have been obtained as metabolic products of a microorganism, in a synthetic manner or by a combination of microbial and chemical procedures (semi-synthetic).

For use in the present invention there comes into consideration any antibiotic substance which is suitable for combating a bacterial infection in a host, including those antibiotics which are only moderately adsorbed when they are not injected or not infused. The most important aspect of the invention lies in its use to enhance the absorption and bioavailability of antibiotics which for the most part can be effectively administered only by injection or infusion because they are not absorbed or are poorly absorbed using other routes of administration.

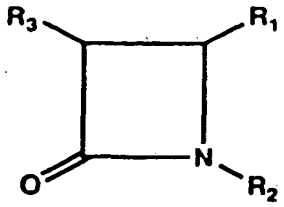
Among the most preferred antibacterial compounds which are used as the therapeutic substance in accordance with the invention are β-lactam antibiotics, especially compounds having a β-lactam ring as the central structure, i.e. the structural element



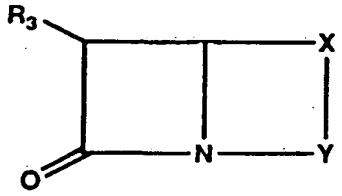
which can be substituted at various positions on the ring or which can be fused with other rings or ring systems which, moreover,

can be substituted or unsubstituted. Examples of such β-lactam antibiotics are penicillins, cephalosporins, penems, carbapenems and monocyclic β-lactams.

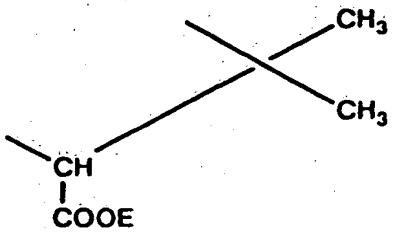
Especially preferred β-lactam antibiotics for use in the present invention are compounds of the formula

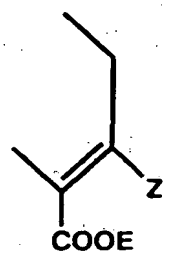


in which R_1 represents hydrogen, alkyl or substituted alkyl, R_2 represents SO_3-M+, M+ represents a proton or a cation, R_3 represents an acylamino group or hydroxyalkyl or R_1 and R_2 together with the β-lactam (azetidinone) ring to which they are bonded represent the group

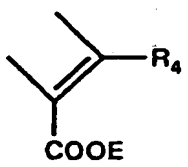


in which X is -S-, -O, -SO-, $-SO_2$, $-CH_2$ or $-CH(CH_3)$ and Y signifies a group

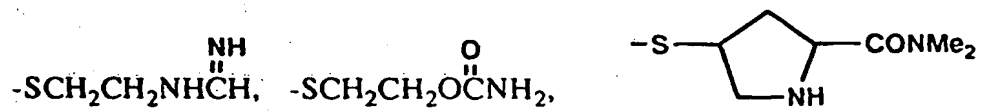




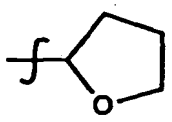
or



in which R_4 represents a substituted thio group such as ethylthio, $-SCH_2CH_2NH_2$,

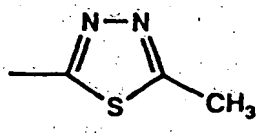


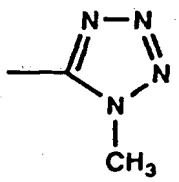
or an optionally substituted lower alkyl group such as aminomethyl, acylaminomethyl,

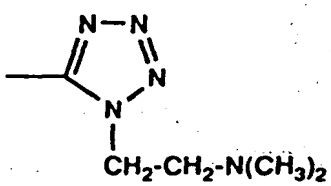


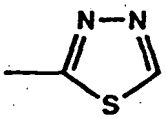
or a substituted oxy group such as carbamoyloxy $(-OCNH_2)$, the C atom which carries the -COOE group is bonded to the nitrogen atoms of the β-lactam ring, Z is hydrogen, halogen, alkoxy or CH_2T, with T denoting hydrogen, alkyl -CO-O-, pyridinium, carboxamidopyridinium, aminopyridinium, carbamoyloxy, azido, cyano, hydroxyl, the group -S-phenyl, which can be substituted, or the group -S-het wherein "het" is an optionally substituted 5- or 6-membered heterocyclic ring, and E represents hydrogen, a pharmaceutically usable ester group or a salt-forming cation.

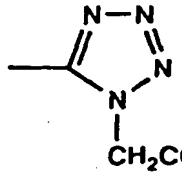
Examples of the 5- or 6-membered heterocyclic rings "het" are the following:

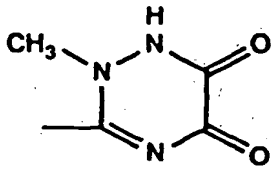












Especially preferred β-lactam antibiotics and their pharmaceutically usable salts, esters and hydrates are ceftriaxone, a cephalosporin which is described in U.S. Patent 4,327,210; carumonam, a monocyclic β-lactam described in European Patent EP 73061; piperacillin, a penicillin described in U.S. Patent 4,112,090; cefamandole, a cephalosporin described in U.S. Patent 3,461,021; mezlocillin, a penicillin described in U.S. Patent 3,974,142; and cefazolin, a cephalosporin described in U.S. Patent 3,516,997. Further examples of such compounds are cefoxitin, cefmetazole, cefotetan, moxalactam, cefuroxime, ceforamide, cefoperazone, ceftizoxime, cefotaxime, cefmenoxime, ceftazidime, cefsulodin, cefazolin, cephalexin, azlocillin, penicillin G, temocillin, sulbenicillin, ticarcillin, mecillinam, amoxicillin, methicillin, carbenicillin, thienamycin, N-formimidoylthienomycin, sulbactam and azthreonam.

Another preferred β-lactam antibiotic for use in the invention is the compound (E)-2-(isobutoxycarbonyl)-2-pentenyl (6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-(azidomethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate which is described in European Patent Publication A2-0318767.

Furthermore, the invention embraces the use of antibiotics which are not β-lactams, for example vancomycin and gentamicin, the adsorption and bioavailability of which are improved using the absorption enhancing system in accordance with the invention.

The material referred to as Laureth-12 is commercially available as MACOL® LA-12 (manufacturer: Mazer Chemical Company, Gurnee, Illinois).

The relative proportions of the two components which are present in the absorption enhancing system in accordance with the invention can be varied in order to achieve optimum results for a particular embodiment of the invention. Preferably, the

weight ratio of (b1) to (b2) lies in the range from 1:50 to 50:1, preferably from 1:10 to 10:1 and most preferably from 1:4 to 4:1.

The effective amount of component (b) in the preparation in accordance with the invention depends on factors such as the particular antibacterial compound which is used and its amount, as well as the age of the patient being treated.

In general, for oral dosage forms it is preferred to use 50 to 1000 mg, especially 100 to 500 mg, of the absorption enhancing system per unit dose of the pharmaceutical preparation. These preparations usually contain the antibacterial compound in amounts of 10 to 500 mg, especially 50 to 200 mg, per unit dose.

Rectal dosage forms usually contain from 50 to 1500 mg, especially 50 to 600 mg, of the absorption enhancing system per unit dose. Such preparations usually contain the antibacterial compound in amounts of 10 to 3000 mg, especially 100 to 1500 mg, per unit dose.

The term "unit dose" is used here in the conventional sense to mean a single administration of the drug in the stated amount. This amount can be administered in the form of a single pill, tablet, capsule or suppository or alternatively in multiples of two or more of such dosage units which together contain the stated amount of drug.

The described antibacterial compound (a) and the components (b1) and (b2) of the absorption enhancing system can be incorporated into a carrier if desired. As the carrier there can be used any pharmaceutically usable solid, semi-solid or liquid carrier in which these components are soluble or readily dispersible. Examples of these are cocoa butter, polyethylene glycols, polypropylene glycols, methylcellulose, carboxymethylcellulose and semi-synthetic bases such as Suppocire® (Gattefosse Corp., Paris). Preferably, the carrier is a solid. Preferred solids for use in accordance with the invention are

mixtures of mono-, di- and triglycerides of C_{12}-C_{18} natural saturated fatty acids, preferably fatty acids having an even number of C atoms (C_{12}, C_{14}, C_{16}). Especially suitable and preferred are pharmaceutical bases of Dynamite Nobel having the trade name "WITEPSOL"®.

Other pharmaceutically compatible carrier materials may be employed as desired depending on particular requirements. Their selection lies within the purview of any person skilled in the art.

When a carrier is utilized, its amounts lie in ranges which are conventional for pharmaceutical carriers materials and which can be safely administered.

An enteric coated formulation, preferably in solid form, is preferred for the oral administration of the preparations in accordance with the invention. The formulation can be filled into hard gelatine or soft gelatine capsules or, where it is liquid, absorbed on to a suitable carrier to form a free-flowing powder and then filled into the capsule or alternatively compressed to pills or tablets. Other dosage forms are microcapsules or beadlets comprising the antibacterial compound and the absorption enhancing system which are encapsulated in a capsule provided with an enteric coating.

The use of enteric coatings serves to protect the anti-bacterial compound from the gastric fluid and to achieve optimum delivery of the antibacterial compound together with the absorption enhancing system to the intestine. The enteric coating is for the most part resistant to and unaffected by the gastric fluid, but dissolves in the intestinal fluid to release the drug.

The effectiveness of a particular enteric coating material can be measured using known procedures. For example, the following are suitable enteric coating materials for use in the present invention:

Cellulose acetate phthalate
cellulose acetate trimellitate
hydroxypropyl methylcellulose phthalate
hydroxypropyl methylcellulose phthalate succinate
polyvinyl acetate phthalate
methacrylic acid
methacrylic acid esters

These materials may be used with or without plasticizers, such as acetylated glycerides or diethyl phthalate, in a manner known per se.

The percentage of coating used is usually between 1 and 10 percent by weight or more, especially between 2 to 8 percent by weight, based on the total weight of the unit dosage form, i.e. the total capsule or the total tablet weight. The following are examples of suitable coating formulations.

Enteric Coating Formulations

Ingredient	Percent by weight
Preparation A:	
Hydroxypropyl methylcellulose phthalate (HPMCP)	5.0
Triacetin	0.5
Methylene chloride	47.25
Denatured alcohol	47.25
Preparation B:	
HPMCP	10.0
Titanium dioxide	0.2
Dimethyl polysiloxane	0.05
Acetone	44.875

Denatured alcohol	44.875

Preparation C:

Cellulose acetate phthalate (CAP)	8.5
Diethyl phthalate	1.5
Titanium dioxide	0.2
Acetone	44.9
Denatured alcohol	44.9

Preparation D:

Polyvinyl acetate phthalate	5.0
Acetylated glycerides	0.8
Methylene chloride	47.1
Denatured alcohol	47.1

Preparation E:

Methacrylic acid or methacrylic acid ester (Eudragit® S or L, Rohm Pharma, GMBH, Wetterstadt, West Germany)	8.0
Acetone	46.0
Anhydrous alcohol	46.0
Plasticizer	q.s.

The oral formulations in accordance with the invention can also contain conventional additives or adjuvants in the amounts which are usual for such materials. For example, such additives can be thickening agents, such as silicic acid (for example Aerosil products), bentonites, colloidal clay, carboxymethyl celluloses, modified montmorillonites, such as alkylammonium salts of montmorillonites (for example commercial products such as Bentone®), organic thickening and structure-forming agents, such as saturated higher fatty acids and alcohols containing 12-20 C atoms (for example stearic and palmitic acid or stearyl and cetyl alcohol), waxes, monoglycerides of saturated or unsaturated high fatty acids such as stearic acid, palmitic acid or oleic acid,

gelling agents, such as aluminium stearate, dispersing agents, such as ionic, non-ionic or cationic surfactants; emulsifying agents, such as lecithin.

The compositions in accordance with the invention can also contain pharmaceutically usable adjuvants, such as binders or lubricants for tabletting, stabilizing agents, antioxidants, flowing agents (to enhance pourability or flowability during processing), preservatives, flavouring agents, colouring agents and buffers. All of these substances can be selected from materials known for such purposes.

The enhanced absorption of antibiotics by mucosal tissue using the preparations in accordance with the invention was investigated in in vivo tests.

Enteral absorption in vivo (rats)

Female rats weighing about 250 g were fasted overnight and anaesthetized with Metofane®. The antibiotics were injected in solution with or without absorption enhancer after incision into the duodenum below the pyloric valve. For purposes of comparison, the solution was alternatively administered intravenously into the tail vein.

Plasma level of the antibiotic in rats

The concentration of the antibiotic in rat plasma was determined at various time intervals after intravenous or enteral administration. Blood samples were collected from the tail vein of each test animal prior to administration of the antibiotic and at 5, 10, 20, 40, 60, 120, 240 and 360 minutes thereafter, then centrifuged and the plasma was frozen until assayed.

Bioassay of plasma samples

Most of the antibiotics tested exhibited some degree of protein binding when the antibiotic-containing plasma was

assayed against the antibiotic in water. Antibiotics which were not bound to plasma were diluted with water and assayed against standards prepared in water. For bound antibiotics, the influence of protein binding was negated by diluting all standard solutions and samples in pooled plasma. In the case of ceftriaxone and cefazolin, the effect of binding was measured by deproteinizing plasma samples with acetonitrile with a dilution factor of 1:12 and assaying against a standard curve diluted in water. Antibiotic levels were determined on agar plates as given below.

Antibiotic	Test organism	Range of standard curves (mcg/ml)	Test media	Volume µl
Carumonam	E. coli. 1346	32-1	AA#1[2]	20
Ampicillin[1]	M. lutea ATCC 9341	8-0.25	AA#1	20
Cefamandole[1]	M. lutea ATCC 9341	32-1	AA#1	20
Cefotaxime[1]	E. coli. 1346	8-0.25 or 16-0.5	AA#1	20
Cefoxitin[1]	S. aureus MB2786	64-4	BHI[3]	20
Ceftriaxone[1]	E. coli. 1346	4-0.125	AA#1	20
Cefazoline[1]	S. aureus ATCC 25923	32-1	AA#1	50
	B. subtilis spores	32-2	AA#1	50
Moxalactam[1]	E.coli. 1346	50-1.56	AA#1	50
Penicillin G[1]	M. lutea ATCC 9341	8-0.5	AA#1	20
Mezlocillin[1]	M. lutea ATCC 9341	16-1	AA#1	50
Gentamicin[1]	K. pneumoniae A	80-2.5	MH[4]	50
Vancomycin[1]	B. cereus ATCC 11778	64-2	AA#8[5]	50

[1] Antibiotics protein bound in rat plasma.
[2] Antibiotic agar # 1 (Difco).
[3] BHI = Brain Heart Infusion Media (Difco).
[4] MH = Mueller Hinton Agar (Difco).
[5] AA#8[5] = antibiotic agar # 8 (Difco).

The plates were incubated overnight at 37°C and the zones of inhibition were read to the nearest 0.1 ml. Calculations were carried out using an autoassay machine (Giles Scientific, Inc., New York). Refer to J. V. Bennett et al., Applied Microbiology 14, 170-177 (1966).

The results were as follows:

Table 1

Enteral absorption in rats
with and without absorption enhancers
Dose = 5 mg/0.5 ml

Cmax (µg/ml)

Antibiotic	(Control) Water	Sodium caprylate (30%) + Laureth-12*
Carumonam	0.0 ± 0.0	6.3 ± 2.4
Cefamandole	1.3 ± 2.5	18.1 ± 3.7
Cefazolin	0.0 ± 0.0	40.7 ± 7.2
Cefoxitin	0.0 ± 0.0	16.2 ± 4.6
Cefotetan	0.0 ± 0.0	26.1 ± 11.4
Gentamicin	3.9	14.1 ± 6.9
Mezlocillin	0.0 ± 0.0	6.7 ± 1.7
Moxalactam	0.0 ± 0.0	19.9 ± 4.5
Penicillin G	0.5 ± 0.1	7.4 ± 2.4
Vancomycin	2.9 ± 0.6	9.8 ± 3.5
Ceftriaxone	2.4 ± 1.9	53.7 ± 13.3

*Weight ratio of other absorption enhancer components to Laureth-12 was 8:1

Oral absorption in vivo (baboons)

Adult baboons (Papio anubis and Papio hamadryas) weighing 12-30 kg were fasted overnight, then sedated by the i.m. injection of ketamine hydrochloride prior to the admini-

stration of the antibiotic. Each baboon received through a gastric tube four hard gelatine capsules each containing 300 mg of ceftriaxone sodium, 200 ml of sodium caprylate, 75 mg of Laureth 12 and 415 mg of Witespol® H15. The bioavailability of this formulation was 15.7±9.9% and 15.0-66.3 µg/ml Cmax range, compared to 0% bioavalibility and 0 µg/ml Cmax for the control (ceftriaxone sodium 300 mg, in the same capsule without absorption enhancer).

Oral absorption in vivo (dogs)

Male beagle hounds weighing 10-14 kg were used in this study and received 2-3 hard gelatine capsules through a gastric tube. The capsules contained 300 mg of cetriaxone sodium, 200 mg of sodium caprylate, 75 mg of Laureth 12 and 415 mg of Witepsol® H15. The bioavailability was 22.4±13.5%, Cmax was 14.4±8.4 µg/ml, compared with 0% and 0 µg/ml for the control (ceftriaxone sodium, in the same capsule without absorption enhancer).

Rectal absorption in vivo (baboons)

Male and female adult baboons (Papio anumbis and Papio hamadryas) weighing 12-27 kg were used in this study and were fasted for 24 hours prior to the administration of the antibiotic, then sedated by the i.m. injection of ketamine hydrochloride prior to the administration of the antibiotic. Suppositories were prepared from the formulations described hereinafter and administered to the animals. The rectal openings were then closed with adhesive tape to prevent expulsion of the suppository mass.

Ceftriaxone Na	600 mg
Laureth 12	125 mg
Na caprylate	200 mg
Witepsol® H15	1075 mg
Total:	2000 mg

In order to measure antibiotic absorption into the bloodstream, blood samples were taken from the femoral region prior to administration of the antibiotic and at 15, 30, 60, 120, 240, 360 and 480 minutes thereafter. Samples were centrifuged and assayed as described above.

The bioavailability was 49.3±13.7%, the Cmax range was 68.1-1002.8 µg/ml, compared with 4.3% bioavailability and 0.3-9.0 µg/ml Cmax range for the control (600 mg of ceftriaxone sodium in the suppository mass without absorption enhancer).

Some formulations for various dosage regimens using the preparations in accordance with the invention are given hereinafter. Although ceftriaxone, the preferred antibiotic in the scope of the invention, figures in these examples, other antibiotics in appropriate amounts can also be used.

ORAL FORMULATIONS

Ceftriaxone (sodium)	60 mg	120 mg	210 mg	300 mg
Sodium caprylate	200 mg	200 mg	200 mg	200 mg
Laureth-12	75 mg	75 mg	75 mg	75 mg
Witepsol® H15	365 mg	365 mg	365 mg	365 mg

RECTAL FORMULATIONS

Ceftriaxone (sodium)	180 mg	300 mg	600 mg	1200 mg
Sodium caprylate	200 mg	200 mg	200 mg	400 mg
Laureth-12	125 mg	125 mg	125 mg	250 mg
Witepsol® H15	1495 mg	1375 mg	1075 mg	2150 mg

The above formulations can be prepared as follows:

Oral formulations

The base (Witepsol® H15) is warmed to 55°C and the components of the absorption enhancer system are admixed with the melt. The melt is then cooled to 45°C and the drug (ceftri-

axone sodium) is added to the molten mass and simultaneously distributed therein. The mass is homogenized until a uniform suspension is obtained. This is then filled into gelatine capsules, sealed if necessary, and the capsules are provided with an enteric coating.

Rectal formulations

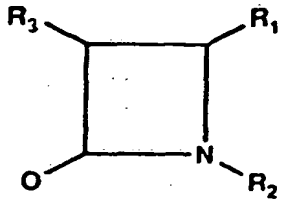
The base (Witepsol® H15) is warmed to 55°C and the components of the absorption enhancer system are admixed with the melt. The melt is then cooled to 45°C and the drug (ceftriaxone sodium) is added to the molten mass and simultaneously distributed therein. The mass is homogenized until a uniform suspension is obtained, then filled into suppository shells and allowed to congeal.

Claims

1. A pharmaceutical preparation containing (a) an antibacterial compound and (b) an effective amount of an absorption enhancing 2-component a system consisting of (b1) polyoxyethylene glycol lauryl ether with 12 ethylene oxide units in the polyoxyethylene glycol part (Laureth-12) and (b2) sodium caprylate.

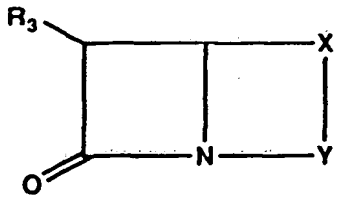
2. A preparation according to claim 1, in which the antibacterial compound is a β-lactam.

3. A preparation according to claim 2, in which the β-lactam has the formula

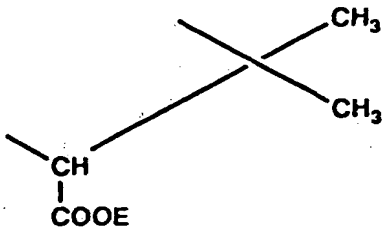


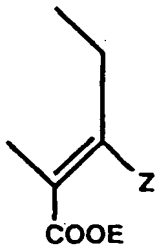
in which R_1 represents hydrogen, alkyl or substituted alkyl, R_2 represents SO_3-M+, M+ represents a proton or a cation, R_3

represents an acylamino group or hydroxyalkyl or R_1 and R_2 together with the β-lactam (azetidinone) ring to which they are bonded represent the group

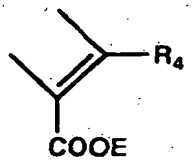


in which X is -S-, -O, -SO-, $-SO_2$, $-CH_2$ or $-CH(CH_3)$ and Y signifies a group



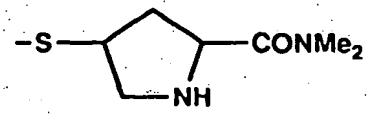


or

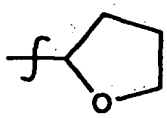


in which R_4 represents a substituted thio group such as ethylthio, $-SCH_2CH_2NH_2$,

$-SCH_2CH_2NHC(=NH)CH$, $-SCH_2CH_2OC(=O)NH_2$,



or an optionally substituted lower alkyl group such as amino-methyl, acylaminomethyl,



or a substituted oxy group such as carbamoyloxy $(-OC(=O)NH_2)$, the C atom which carries the -COOE group is bonded to the nitrogen atom of the β-lactam ring, Z is hydrogen, halogen, alkoxy or CH_2T, with T denoting hydrogen, alkyl -CO-O-, pyridinium, carboxamido-

pyridinium, aminopyridinium, carbamoyloxy, azido, cyano, hydroxyl, the group -S-phenyl, which can be substituted, or the group -S-het, wherein "het" is an optionally substituted 5- or 6-membered heterocyclic ring, and E represents hydrogen, a pharmaceutically usable ester group or a salt-forming cation.

4. A preparation according to claim 2, in which the antibacterial compound is (E)-2-(isobutoxycarbonyl)-2-pentenyl (6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-(azidomethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

5. A preparation according to claim 2, in which the antibacterial compound is ceftriaxone or a pharmaceutically usable salt, ester or hydrate thereof.

6. A preparation according to any one of claims 1-5 in an enteric coated oral dosage form.

7. A preparation according to any one of claims 1-5 in a rectal dosage form.

8. A pharmaceutical preparation according to claim 1, substantially as hereinbefore described.

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AGENTS FOR THE APPLICANTS.

A pharmaceutical preparation for improving the resorption of anti-bacterial components

Legal status (INPADOC) of **IE63119**

IE	**F**	**371889 A**	(Patent of invention)
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	PRS Code :	MM4A	
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